REMARKS

Claims 24-27, 31-68, and 70-94 are currently pending in the application. Claims 1-63 are cancelled. The amendments find support in the specification and are discussed in the relevant sections below. In addition, amendments to the claims have been made to insert Sequence Identifiers, in response to the Communication of 27 September 2007. No new matter is added.

At the outset, Applicants would like to thank Examiners Hutson and Achutamurthy and TQAS Eyler for taking the time to discuss the instant application with Applicants' representatives on December 19, 2006. The substance of discussion that took place during the interview is discussed herein below.

Rejection of Claims 64-94 Under 35 U.S.C. §112, Second Paragraph

The Office Action states that claims 64-94 are rejected under § 112, second paragraph for alleged indefiniteness. In particular the Office Action rejects the claims on the grounds that the phrase "DNA polymerization activity of a DNA polymerase or reverse transcriptase" renders the claims indefinite. While not acquiescing to the rejection, Applicants have amended the claims to recite "5' - 3' polymerization activity of a DNA polymerase or reverse transcriptase".

It is well settled law that the primary purpose of the definiteness requirement under § 112, second paragraph, is to ensure that the scope of the claim is clear so that the public is informed of the boundaries of what constitutes infringement of the patent (MPEP 2173). This primary question is whether the claims are clear, not whether "more suitable language or modes of expression are available" (MPEP 2173.02). As amended the claims recite a first enzyme having

5' - 3' polymerization activity of a DNA polymerase or reverse transcriptase. It is well known in the art, and described in the specification that polynucleotide polymerases catalyze the polymerization of nucleotides generally initiating synthesis at the 3' end of the primer and proceeding toward the 5' end of the template strand (Page 9). Both DNA polymerase and reverse transcriptases are known to have 5' - 3' polymerization activity; that is, they can catalyze the 5' - 3' polymerization of a new nucleic acid strand.

The metes and bounds of the claims are clear. Enzymes that fall under the claims are those that have the 5' - 3' polymerization activity that is possessed by either a DNA polymerase or reverse transcriptase. There is no ambiguity as to what is encompassed by this claim limitation. In addition, during the examiner interview of December 19, 2006, Applicants proposed the current claim language with respect to 5' - 3' polymerization activity, and Examiner Hutson indicated that this amendment should be sufficient to overcome the rejection.

Applicants accordingly request that the rejections be reconsidered and withdrawn.

Rejection of Claims 64-94 Under 35 U.S.C. § 112, First Paragraph

Written Description

The Office Action states that claims 64-94 are rejected under § 112, first paragraph for allegedly containing subject matter that is not supported by the specification at the time of filing. The Office Action states that the claimed combination of Archaeal DNA polymerase and mutant Archaeal DNA polymerase comprising a 3' - 5' exonuclease activity and a reduced DNA polymerization activity is not supported by the specification. The claims were amended in

Applicants prior response, filed on August 11, 2006, such that they do not refer to a combination of Archaeal DNA polymerase and mutant Archaeal DNA polymerase. Applicants accordingly request that this portion of the rejection be withdrawn.

The Office Action states that claims 64-94 are also rejected under § 112, first paragraph for allegedly failing to comply with the written description requirement for the recitation of a first enzyme that comprises "a DNA polymerization activity". The Office Action states that such activity may include activities in addition to "DNA polymerization activity itself", such as DNA binding activity, dNTP binding activity, helicase activity, etc. The Office Action concludes that Applicants have not adequately described those enzymes that comprise the breadth of those activities. Applicants respectfully traverse the rejection.

As amended, the claims recite a first enzyme comprising "5' - 3' polymerization activity of a DNA polymerase or reverse transcriptase", thus, clarifying that the activity possessed by the claimed enzyme is the DNA polymerization activity itself. The specification teaches (Page 1) that all DNA polymerases possess 5' - 3' DNA polymerization activity and, further, specifically teaches over 30 examples of enzymes that possess the 5' - 3' DNA polymerization activity of a DNA polymerase or reverse transcriptase.

Based on the disclosure in the specification and state of the art at the time the instant application was filed, Applicants have demonstrated that they were in possession of the invention recited in the amended claims and, accordingly, request that the rejection be reconsidered and withdrawn.

Enablement

The Office Action states that claims 64-84 are rejected under §112, first paragraph, for alleged overbreadth. The Office Action states that the specification does not provide sufficient teachings to enable one of skill in the art to practice the claimed invention with any enzyme mixture comprising a first enzyme with a polymerization activity of a DNA polymerase or reverse transcriptase and a second enzyme comprising a mutant Archaeal DNA polymerase comprising one or more mutations selected from Y410, T542, D543, K593, Y595, Y385, G387, and G388. Applicants respectfully disagree and traverse the rejection.

With respect to the enablement of a first enzyme having a DNA polymerization activity of a DNA polymerase or reverse transcriptase, as noted above, Applicants have amended the claims to recite that the first enzyme has 5' - 3' activity of a DNA polymerase or reverse transcriptase. The instant specification teaches, and it is well known in the art that 5' - 3' polymerization activity is possessed by all DNA polymerases. Thus, between the teachings in the specification and the general knowledge in the art, Applicants have enabled numerous species of first enzymes having 5' - 3' DNA polymerization activity, such that one of skill in the art could readily practice the invention with respect to the first enzyme without having to engage in undue experimentation.

The Office Action also states that the claims are rejected with respect to the second enzyme, originally claimed as a mutant Archaeal DNA polymerase comprising selected mutations. The instant claims have been amended, however, to delete reference to a mutant Archaeal DNA polymerase. Instead, the claims recite that the second enzyme is a DNA

polymerase comprising the partitioning domain sequence YXGG, the polymerase domain sequence DXXSLYP, the polymerase domain sequence YIDTDG, and the polymerase domain sequence KXY, and that the second enzyme has reduced 5' - 3' DNA polymerization activity. The specification teaches that these partitioning and polymerase domain sequences are common to a number of Archaeal DNA polymerases, including Pfu, Tgo, KOD, Tli, and Deep Vent (see page 27-29). In addition, Applicants have compared the sequences of those Family B DNA polymerases taught in the specification at pages 14-19, and found that the now claimed domain sequences (or minor variants thereof) are found in each of the polymerases taught. Moreover, the prior art, known at the time the instant application was filed, teaches that the recited domain sequences (or consensus sequences thereof) are common to an even larger number of Archaeal DNA polymerases, including S. *solfataricus* MT4, S. *solfataricus* P2, S. *acidocaldarius, Thermococcus* 9oN-7, *Methanococcus voltae,* and *Methanococcus jannaschi* (see, e.g., Edgell et al. 1997, J. Bacteriology 179:2632; Hopfner et al., 1999 Proc. Nati. Acad. Sci. 96:3600), in addition to those taught in the specification. Thus, the amended claims not place clear structural limitations on the claimed second enzyme, regardless of what mutations other than those specifically recited, may be encompassed by the use of the phrase "comprising an amino acid substitution".

During Applicants' interview with the Examiner (as well as the Examiner's supervisor and TQAS Bonnie Eyler), the Examiner and TQAS Eyler articulated that the basis for the current rejections was the phrasing "comprising a mutation". They indicated that this language, while making clear that the second enzyme had to include at least one of the specified mutations, left

room for additional, undescribed mutations. Thus, because the claims were originally drawn to an "Archaeal DNA polymerase" or "Pfu DNA polymerase", or KOD, Tgo, Deep Vent, Tli, or JDF-3 DNA polymerase, the ultimate question was: how far could you mutate the sequences of the recited polymerases (based on the "comprising a mutation" language) before the polymerase ceased to be an Archaeal, Pfu, KOD, Tgo, Deep Vent, Tli, or JDF-3 DNA polymerase. As amended the claims no longer recite a phylogenetic label for the second enzyme. That is, the claims no longer recite, for example, an Archaeal DNA polymerase. Instead, the claims have been amended to recite that the second enzyme is a "DNA polymerase" having specific structural elements, and reduced 5' - 3' DNA polymerization activity. Thus, the question of when an Archaeal DNA polymerase is mutated so far as to cease being classified as an Archaeal DNA polymerase is moot. The second enzyme is now required to be a DNA polymerase including the partitioning domain sequence YXGG, the polymerase domain sequence DXXSLYP, the polymerase domain sequence YIDTDG, and the polymerase domain sequence KXY. Thus, as long as the second enzyme is a DNA polymerase (comprising at least one of the recited substitutions and having 3' exonuclease and reduced 5' - 3' polymerization activity) and is from the specified division of organisms (see, claims 71, 76, 77, 78, 80, 81, 89, 91,93, 95, 96, and 97), it would fall under the claims.

The claims recite, and the specification teaches, specific sites of mutation that result in a second enzyme that is able to catalyze the polymerization of deoxynucleotides, but that also has reduced 5' - 3' DNA polymerization activity. The specification specifically teaches 65 mutant polymerase domain and partitioning domain sequences across five different DNA polymerases

that fall under the claim (see, Tables 2A and 2B). The fact that one of skill in the art may make additional mutations outside the claimed region in an effort to generate a DNA polymerase with reduced 5' - 3' DNA polymerization activity is not fatal to the enablement of the instant claims.

While the instant claims no longer specifically recite an Archaeal DNA polymerase, the recited domain sequences are common across numerous members of the Archaeal DNA polymerase family. It was well known in the art at the time the instant application was filed that members of the family of Archaeal DNA polymerases share common sequence motifs and domains that possess particular function. For example,

- Edgell et al. shows sequence alignments of 15 different Archaeal DNA polymerases, and identifies three exonuclease domains and seven polymerase domains, that play a role, respectively, in the exonuclease and polymerization activity of the Archaeal DNA polymerases (Edgell et al., 1997 J. Bacteriol. 179:2632).
- Hopfner et al. teaches that the Archaeal DNA polymerases share a DTDG motif in the polymerase active site (Hopfner et al., 1999, PNAS 96:3600).
- Wang et al. prepared a sequence alignment of 24 Family B DNA polymerases, of which the Archaeal DNA polymerases are a subfamily, and teaches that the alignment shows 10 absolutely conserved and 96 consensus residues, three quarters of which "appear to play a role in the enzyme's structural integrity, while one-quarter may be directly involved in binding the dNTP and DNA primer-template substrates, as well as binding the metal ions required for

both exonuclease and polymerase catalytic activities" (Wang et al., 1997, Cell 89: 1087).

- The specification provides specific guidance as to where mutations could be made in a DNA polymerase to reduce polymerization activity. For example, the specification teaches at page 21-22 that mutations in the partitioning and polymerase domains are likely to result in reduced polymerization activity.
- The specification also teaches that several investigators had already identified DNA polymerase mutations that selectively reduce DNA polymerization activity (Blanco et al., 1995 Methods of Enzymology 262:283-294 ((Bacteriophage 429); Truniger et al., 1996, EMBO J. 15:3430-3441 (Bacteriophage 429); Abdus Sattar et al., 1996, Biochemistry 35:16621-9 (Bacteriophage T4); Tuske et al., 2000, J. Biological Chemistry 275:23759-68 (Kienow fragment); Bohlke Ct al., 2000, Nucleic Acid Research 28:3910-3917 (Thermococcus aggregans); Pisani et al., 1998, Biochemistry 37:15005-15012 (Sulfolobus solfataricus); Komori Ct al., 2000, Protein Eng 13:41-7 (Pyrococcus furiosus); Shen et al., 2001 J. Biological Chemistry 276:27376-83 (Pyrococcus horikoshi Family D); these mutations being different from those recited in the instant claims).

Thus, the level of skill in the art relating to DNA polymerases comprising the recited domain sequences at the time the instant application was filed was high. One of skill in the art seeking to introduce an amino acid substitution in a second enzyme, other than at the claimed

positions, would have had ample guidance from the state of the art as to what domains, regions, or specific sequences of a DNA polymerase comprising the recited domain sequences would have been a good candidate for modification to arrive at a DNA polymerase with 3' exonuclease activity and reduced 5' polymerase activity. In addition, the specification also teaches methods for one of skill in the art to measure 5' - 3' DNA polymerization activity and 3' exonuclease activity of a DNA polymerase (pages 29-33). Accordingly, the specification teaches numerous examples of second enzymes comprising one or more of the recited amino acid substitutions, and the specification combined with the knowledge and skill in the art, would permit one of skill in the art to make additional amino acid substitutions outside the specified positions and determine if such substitutions resulted in a DNA polymerase (*i.e.*, having the ability to catalyze the polymerization of deoxyribonucleic acid) having 3' exonuclease activity and reduced 5' - 3' polymerization activity without resorting to undue experimentation.

Accordingly, the instant claims are enabled by the teachings of the specification and the general level of knowledge and skill in the art, and Applicants therefore request that the rejections be reconsidered and withdrawn.

Rejection of Claims 64-66, 68, 71, 73, 75, 79, 85, 87, 89, 91, and 93 Under 35 U.S.C. § 1O3

The Office Action states that claims 64-66, 68, 71, 73, 75, 79, 85, 87, 89, 91, and 93 are rejected under §103 as unpatentable over Barnes et al. and Komori et al. The Office Action states that Barnes et al. teaches a number of thermostable DNA polymerase mutants and formulations of polymerases comprising a thermostable DNA polymerase lacking 3' exonuclease

activity and at least one thermostable DNA polymerase exhibiting 3' exonuclease activity with diminished polymerase activity. The Office Action states that Komori et al. teach a D405E mutation in Pfu DNA polymerase that results in decreased polymerase activity. The Office Action concludes that it would have been obvious to use the polymerase mutations taught by Komori et al. in the formulation taught by Barnes et al. to catalyze the amplification of unusually long and faithful DNA products.

While not acquiescing to the rejection, Applicants have amended the claims to exclude the D405 amino acid substitution from the second enzyme. There is no teaching or suggestion in either Barnes et al. or Komori et al. to include the additional amino acid substitutions recited in the claims in Pfu or any other DNA polymerase. Thus, even if combined as suggested by the Office Action, the teachings of Barnes et al. and Komori et al. to not teach or suggest each of the limitations of the amended claims. Applicants accordingly request that the rejection be reconsidered and withdrawn.

Double Patenting

The Office Action states that claims 64-94 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 6, 9-14, 18, 20-22, and 36-51 of co-pending application USSN 10/035,091. Applicants will timely submit a terminal disclaimer to disclaim any term of the instant application that would extend beyond the expiration of the 10/035,091 application upon notification of allowable subject matter in the instant case, and upon confirmation that the claims, at that time, are patentably indistinct.

Conclusion

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 50-3740.

Respectfully submitted,
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Date: 22 October 2007

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